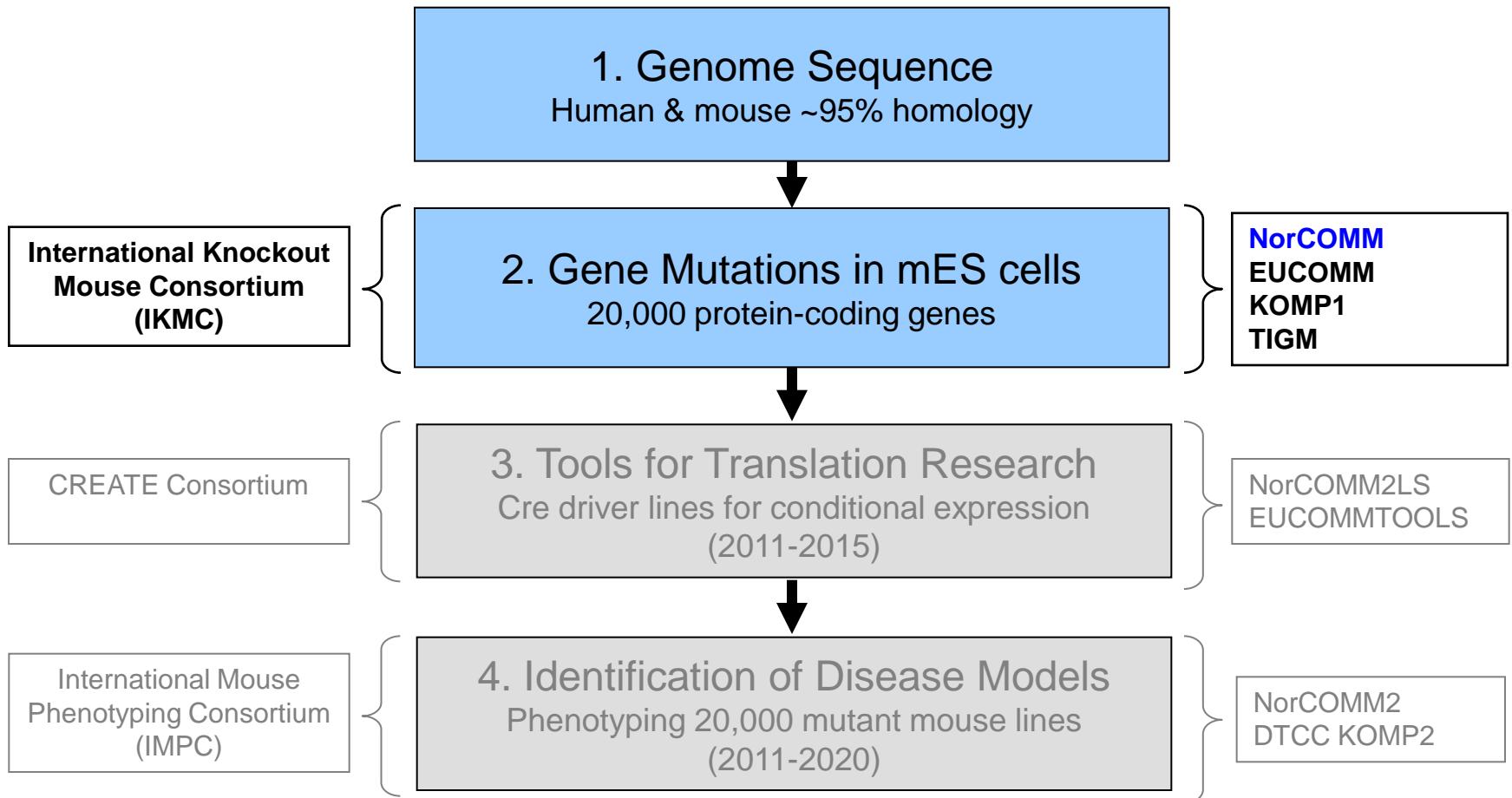
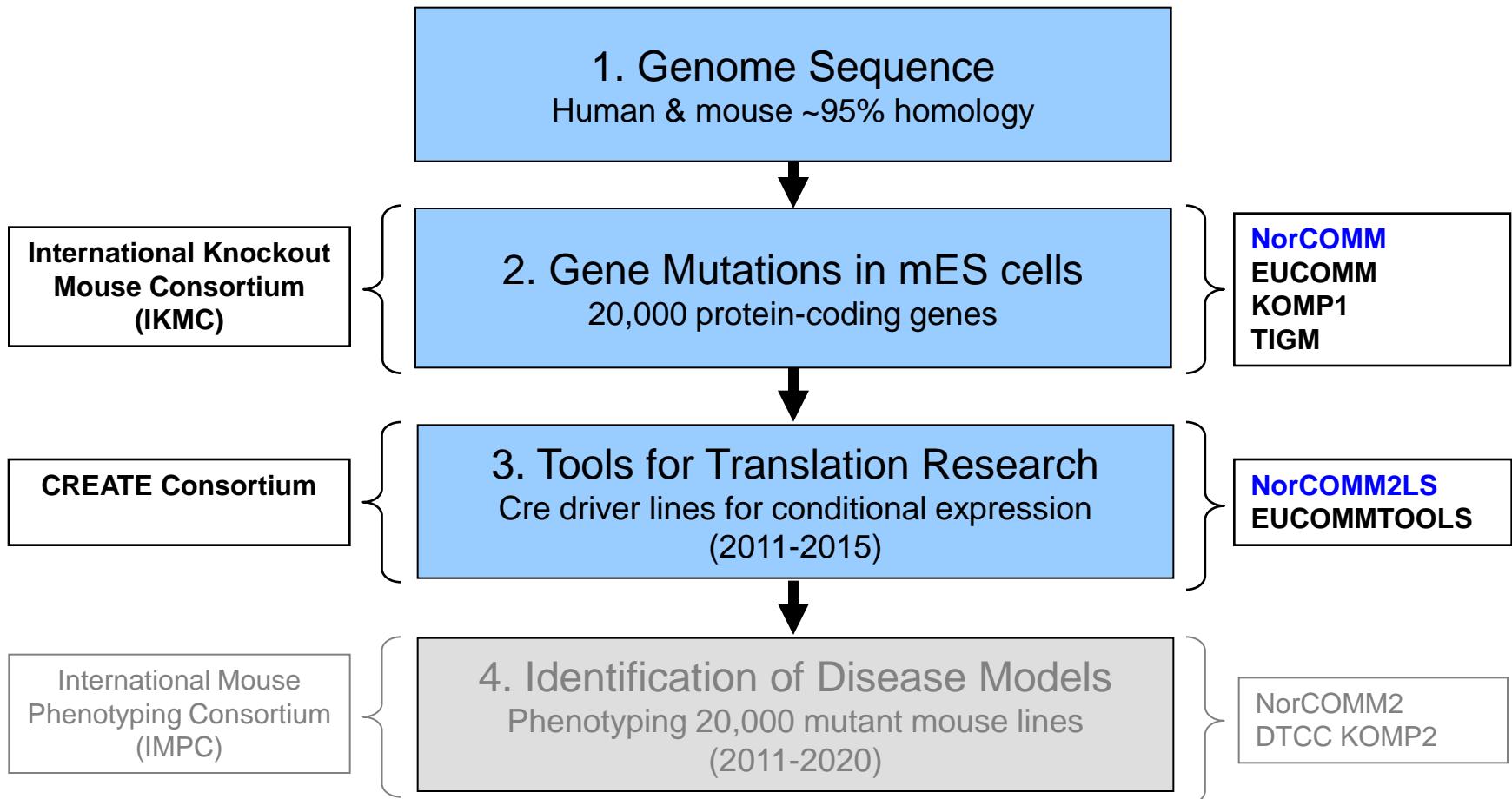
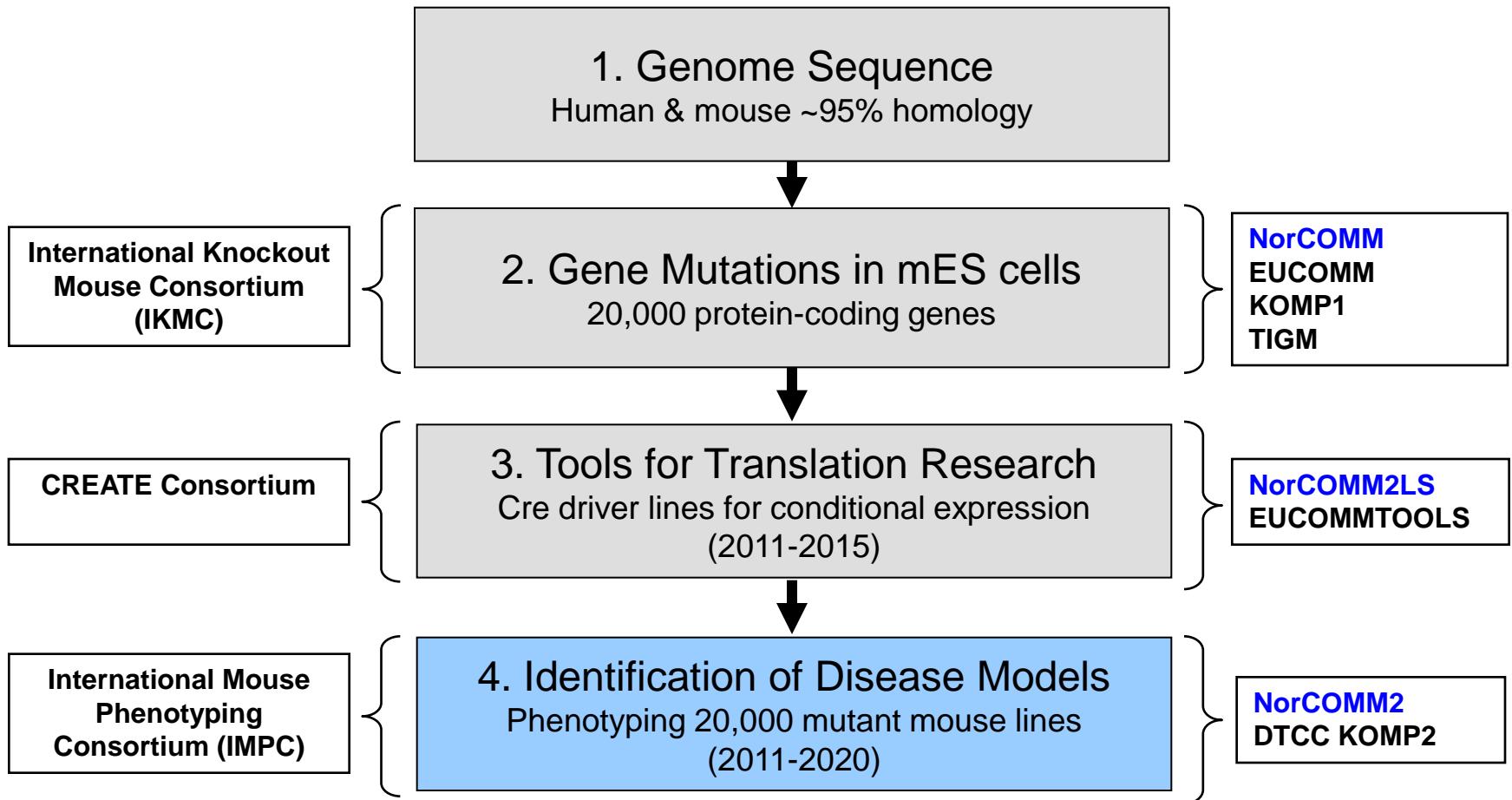


TCP mouse model production and phenotyping for functional annotation of the genome









Two Infrastructure Support Programs

- TCP Research & Facility Operations
 - Animal holding and facilities for PI-driven research
 - Animal holding to support Research Programs at TCP
- TCP Transgenic Core
 - Transgenic & knockout production, embryo biology



Three Research Programs

- Centre for Modeling Human Disease (CMHD)
 - Random & targeted mutagenesis
 - Physiology and Neurobiology phenotyping
 - Pathology (Gross, Histology, Molecular) phenotyping
- Canadian Mouse Mutant Repository (CMMR)
 - Cryopreservation & archiving services for mouselines
 - IVF for recovery and storage of mouselines
 - National repository for ILMC
- Mouse Imaging Centre (MICE)
 - Multi-modality mouse imaging collaborations



NorCOMM2 Project Objectives



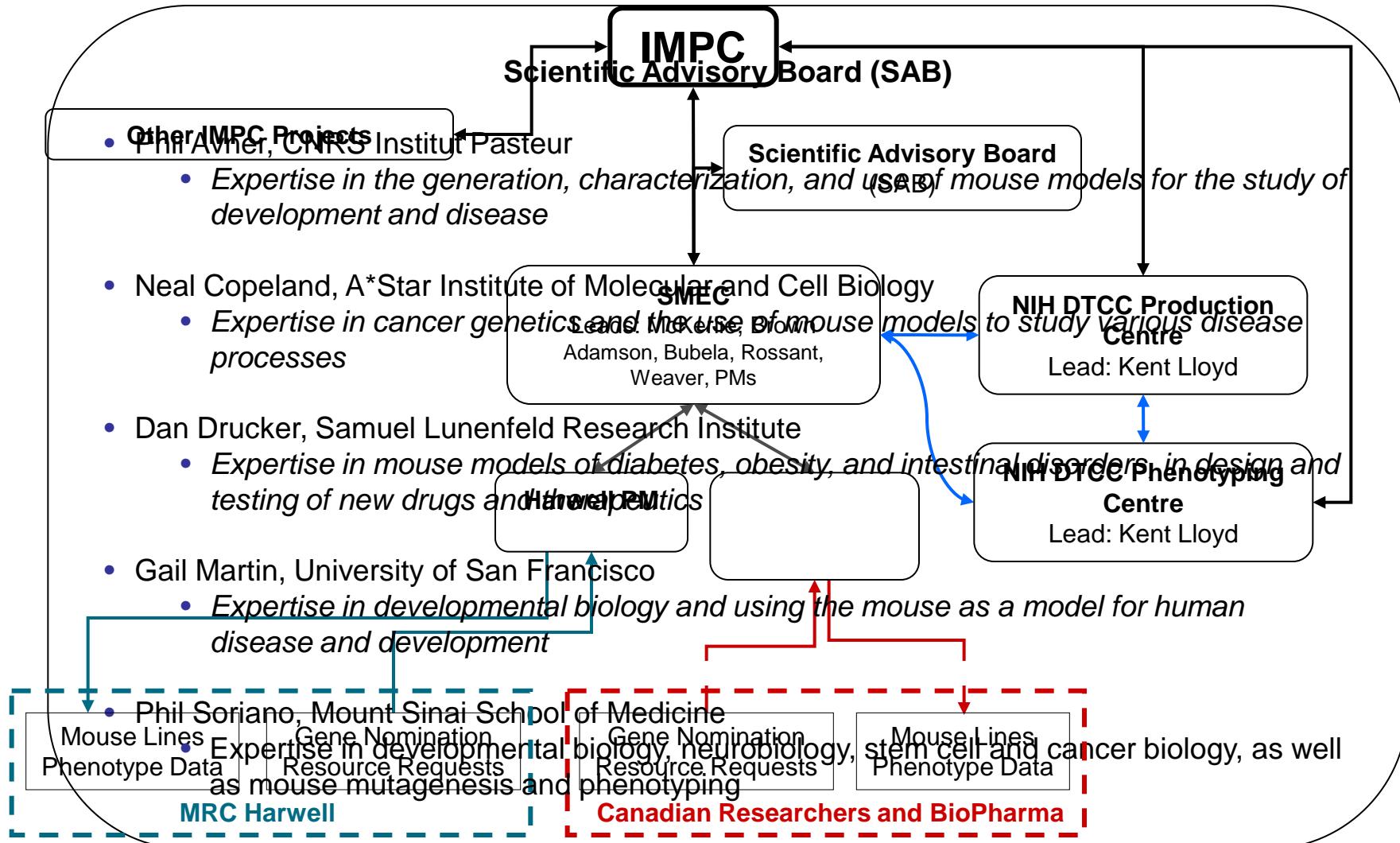
NorCOMM2 Production & Cryopreservation

| Production Year | TCP Morula Aggregation | MRC Harwell Blast Injection | Total |
|-----------------|------------------------|-----------------------------|-------|
| Y01 | 65 | 66 | 111 |
| Y02 | 85 | 82 | 132 |
| Y03 | 0 | 82 | 132 |
| Y04 | 0 | 99 | 99 |
| Y05 | 0 | 0 | 0 |
| | 150 | 330 | 480 |

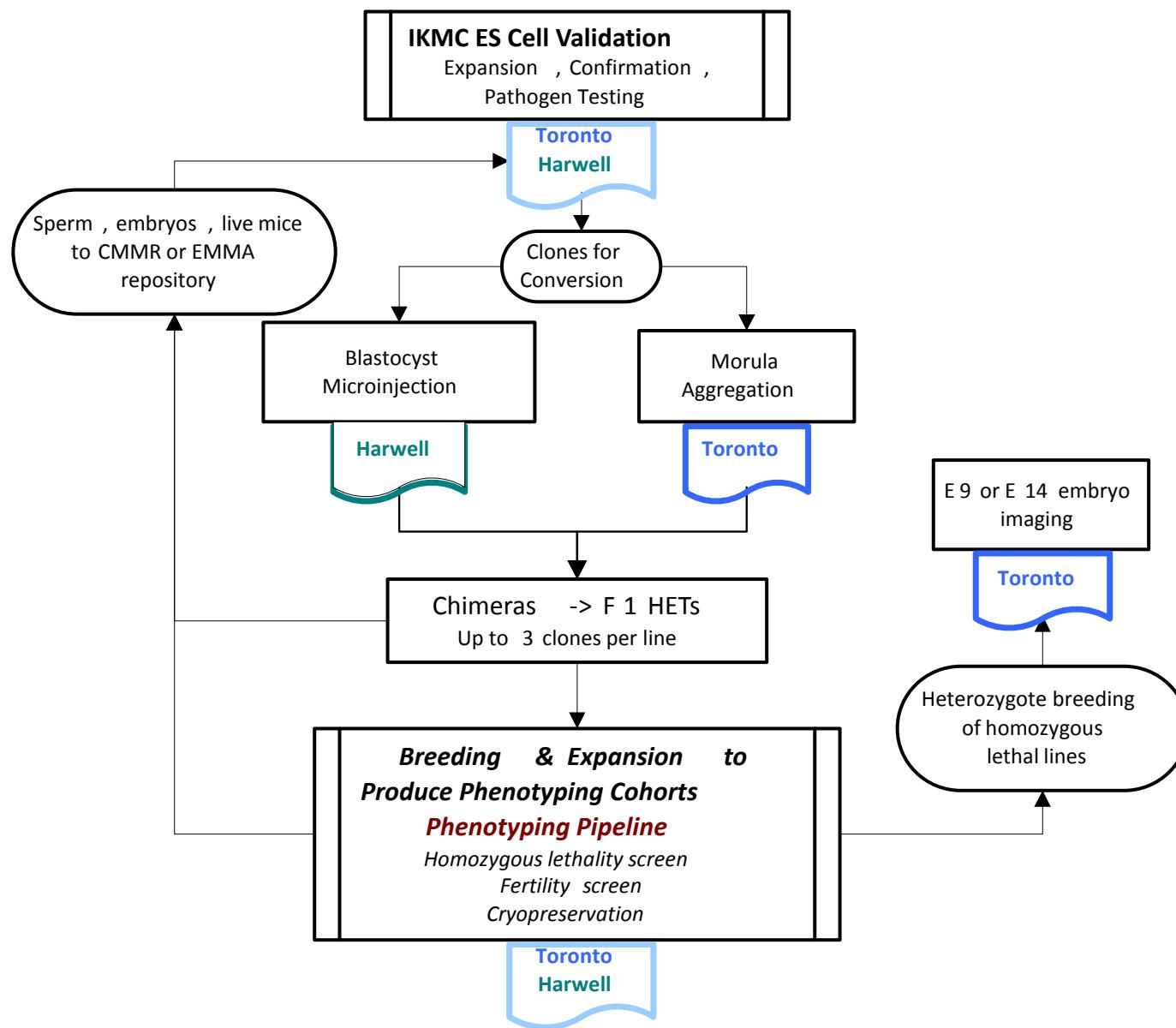
NorCOMM2 Phenotyping

| Phenotyping Year | TCP Adult HOM / Adult HET / Subviable | MRC Harwell Adult HOM | Total Adult HOM + Subviable |
|------------------|---------------------------------------|-----------------------|-----------------------------|
| Y01 | 0 | 0 | 50 |
| Y02 | 45 / 30 / 30 | 80 | 130 |
| Y03 | 45 / 30 / 30 | 82 | 132 |
| Y04 | 0 | 82 | 82 |
| Y05 | 0 | 86 | 86 |
| | 150 | 330 | 480 |

NorCOMM2 Project Coordination



NorCOMM2 Project Workflow



NorCOMM2 Gene Selection



North American Conditional Mouse Mutagenesis Project 2

[Home](#)[Nominate Genes](#)[Project](#)[The Pipeline](#)[Gene List](#)[Links](#)[Contact Us](#)[Log in](#)[Create new account](#)

The opportunity ...

Do you have one or more gene candidates for disease, development, or drug target validation, but you don't have enough data to write that grant proposal or explore gene function? Then this site is for you!

- NorCOMM2 is part of an international consortium to functionally annotate all 20,000 genes of the mammalian genome in the next 10 years ([more info...](#))
- NorCOMM2 will generate and phenotype 150 new knock-out mouse lines over three years to identify gene function and new models of human disease ([see the pipeline...](#))
- We prefer to do genes for which Canadian scientists want mouselines and data.
- We will prioritize genes for mouse line production & phenotyping that
 - Are nominated by Canadian scientists
 - Have no published existing knock-out
 - Have not been phenotyped by another centre in the consortium
 - Have ES cell line(s) available from the International Knockout Mouse Consortium resource
 - Are relatively unannotated

[Nominate Genes](#)

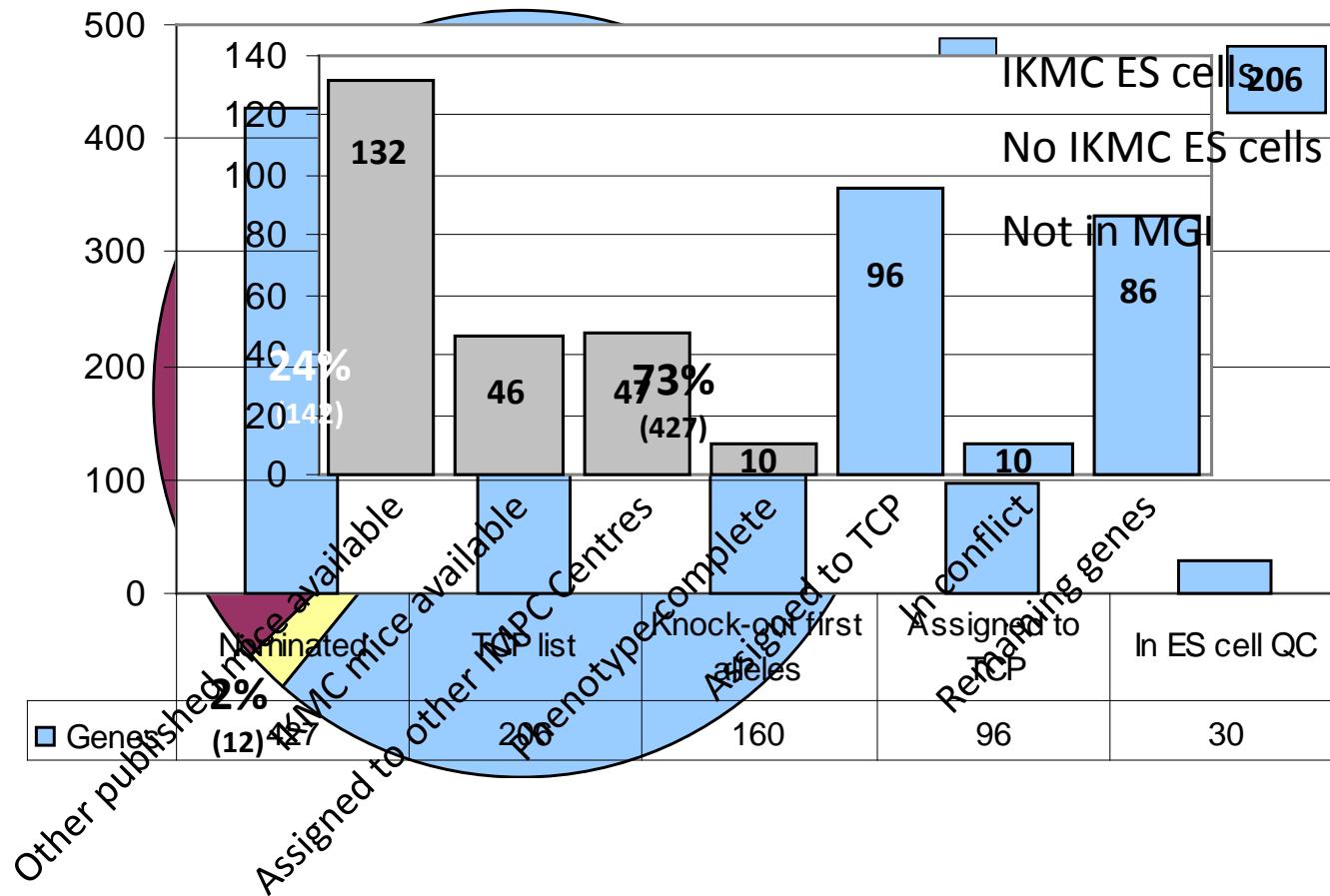
copyright © 2011 Toronto Centre for Phenogenomics (TCP)

"This work was funded by the Government of Canada through Genome Canada and the Ontario Genomics Institute (OGI-051)"

Genes Nominated to NorCOMM2.org



- 581 unique gene nominations from Canadian scientists and 3 consortia
 - Ontario Institute for Cancer Research
 - Cystic Fibrosis Modifier Gene Consortium
 - Lysosomal Storage Research Group



NorCOMM2 Gene Selection



North American Conditional Mouse Mutagenesis Project 2

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The Pipeline

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Colin McKerlie

:: Settings ::

Your Gene List ...

| Gene | Status |
|---------|-----------------------------|
| pstpip1 | No IKMC ES cell line |
| pstpip2 | No IKMC ES cell line |
| Lpin2 | ES cell line QC in progress |
| Mvk | No IKMC ES cell line |

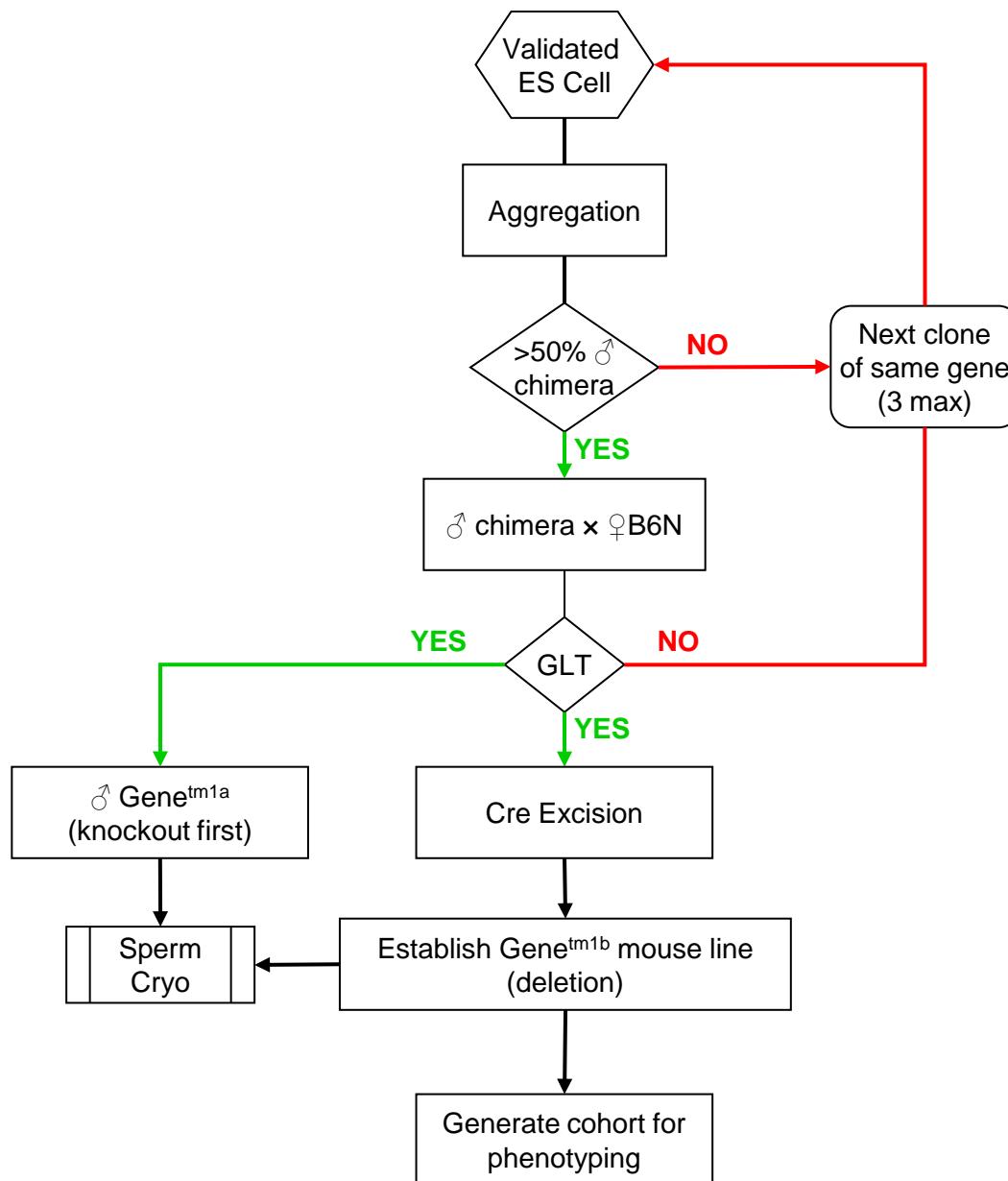
[Nominate Genes](#)

Statistics ...

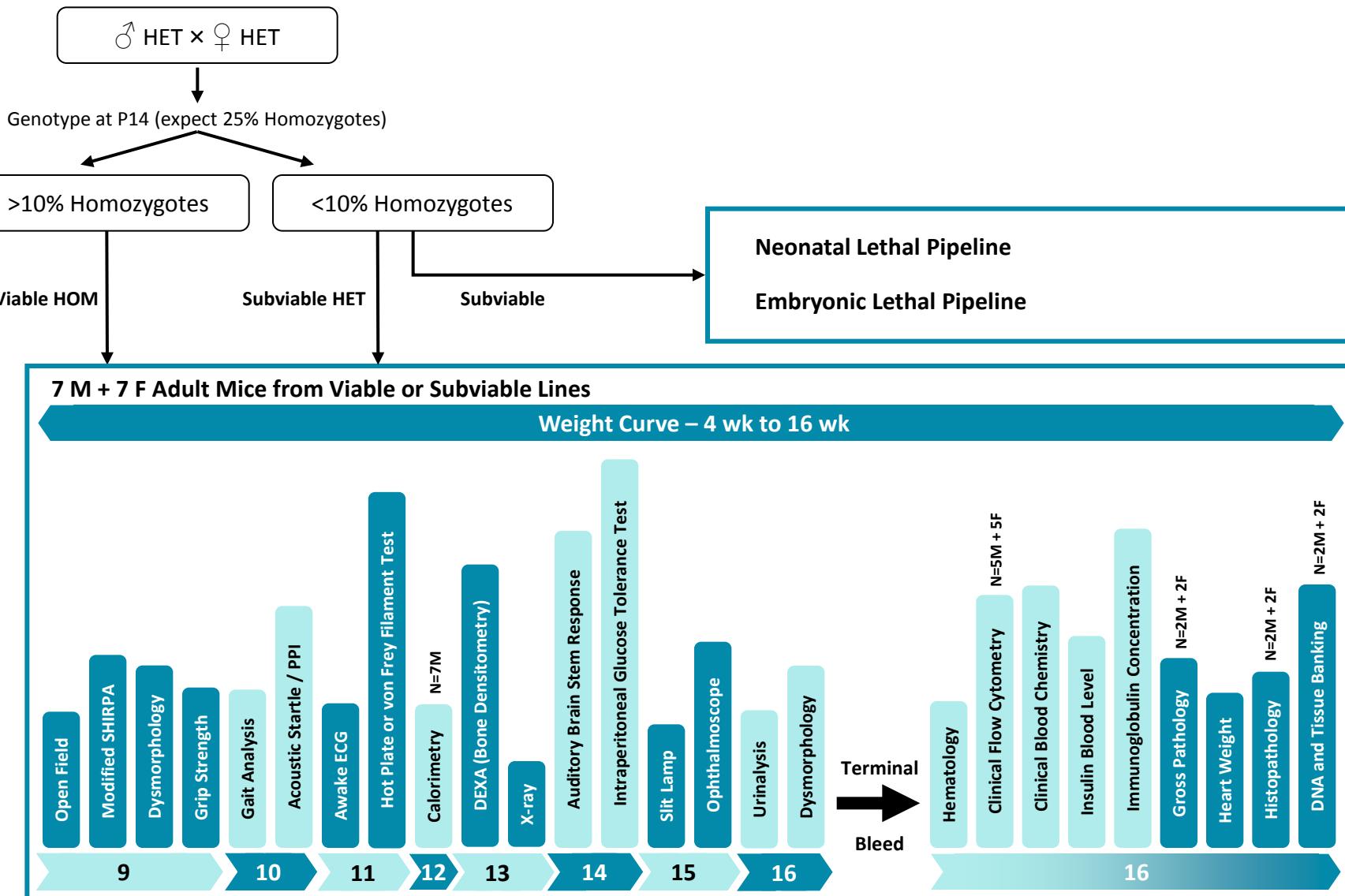
We have a total of 587 genes nominated by 40 researchers.
NorCOMM2 is funded to produce and phenotype 150 mouselines.

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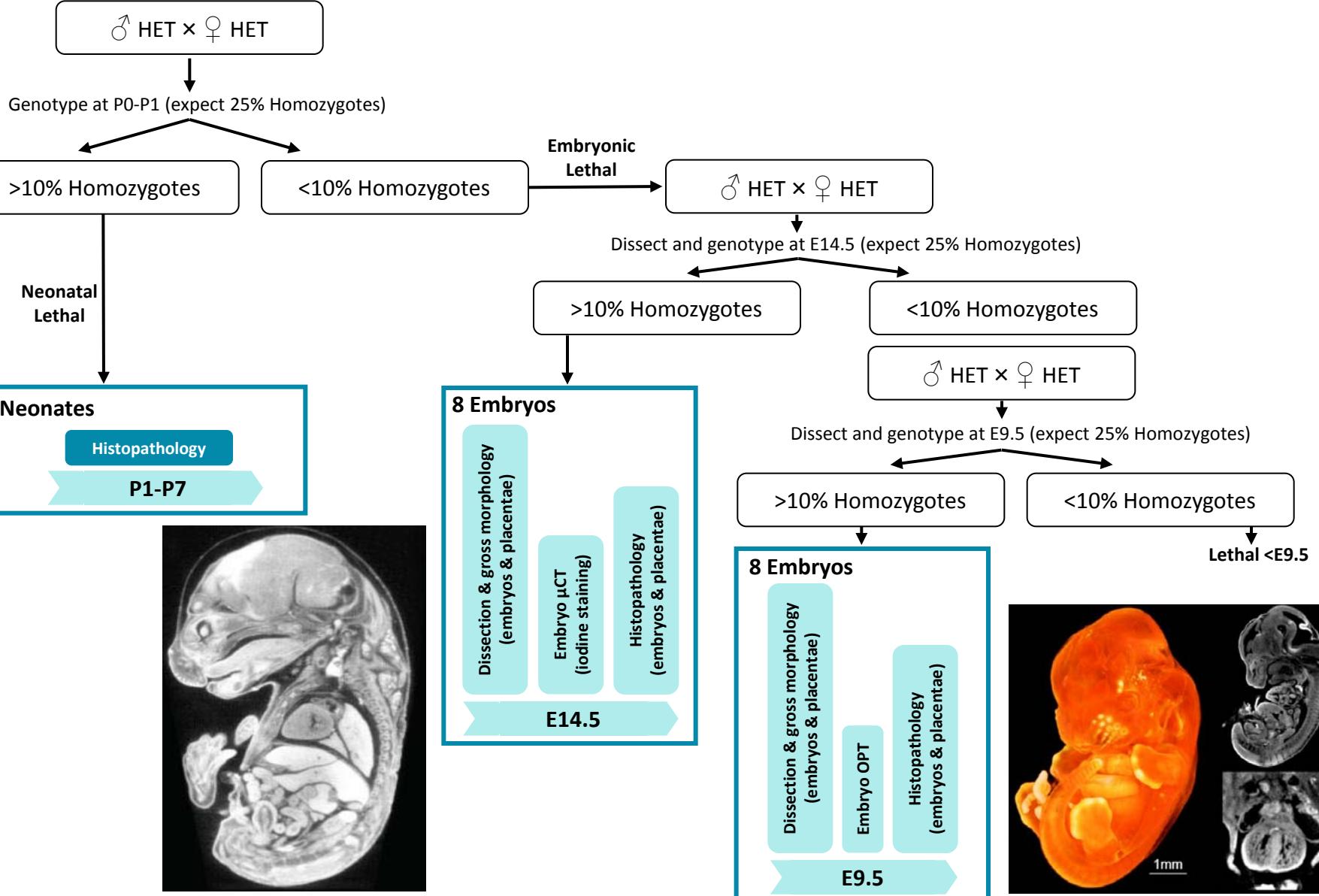
NorCOMM2 Production Flowchart



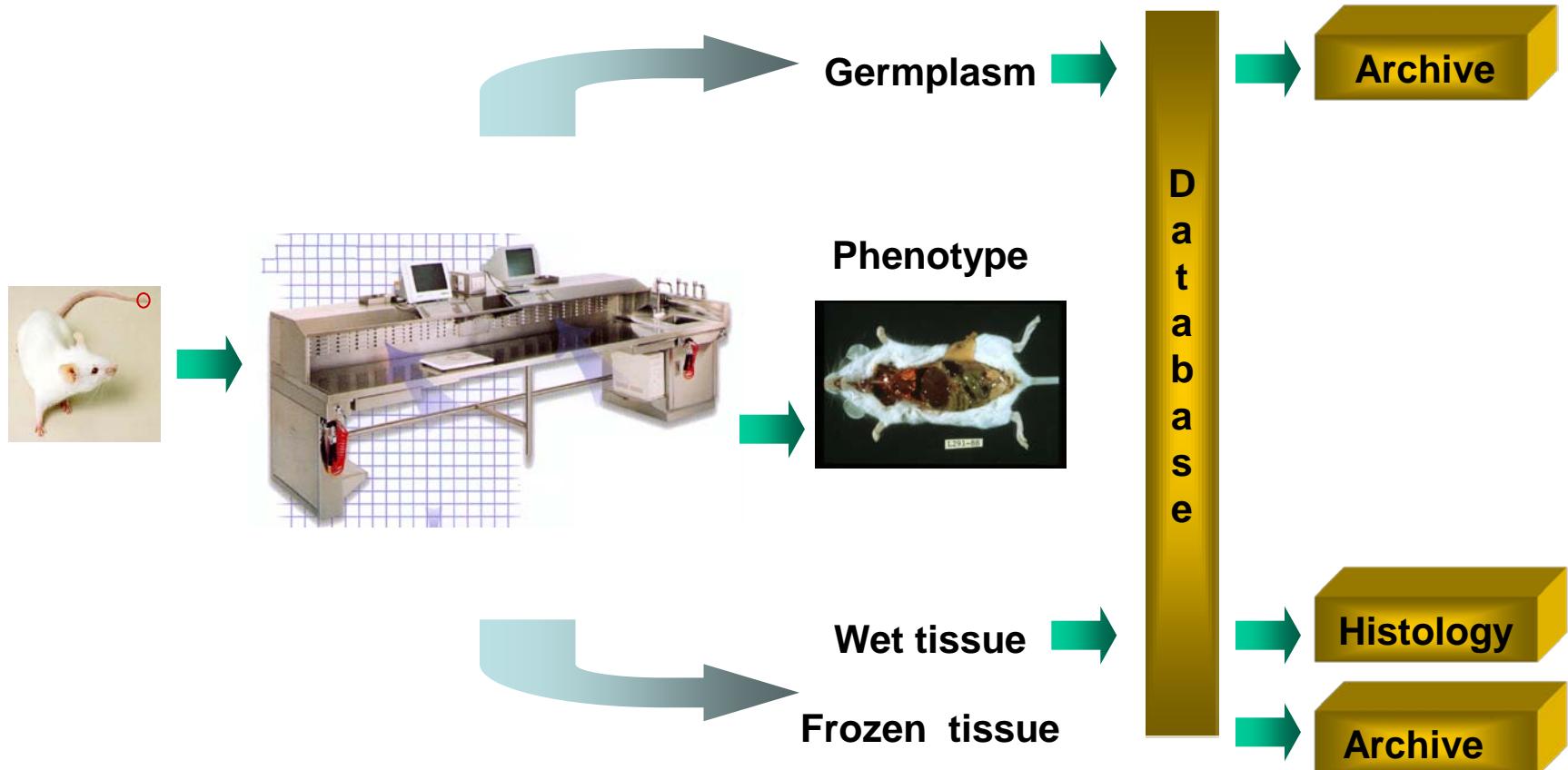
NorCOMM2 Adult Phenotyping



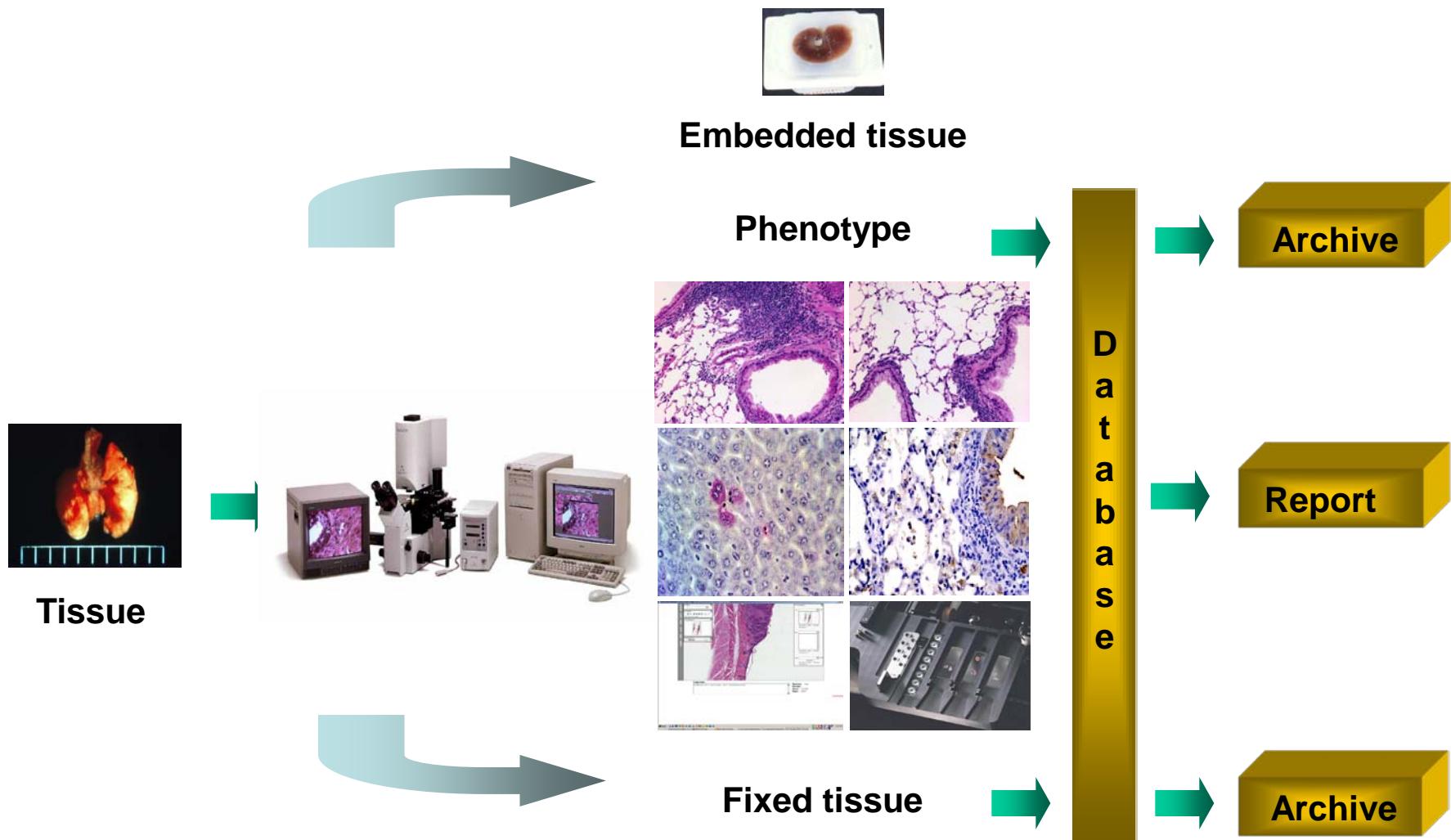
NorCOMM2 Neonate & Embryo Phenotyping



Pathology Phenotyping at TCP



Pathology Phenotyping at TCP



Project Design

1. Sanger MGP tissue collection
 - 30 tissues collected from each of 2M + 2F, fixed in 10% NBF, then embedded in 14 tissue blocks
2. TCP tissue preparation
 - Cut 5µm sections from each block and stain with H&E
3. TCP tissue evaluation
 - Complete histopathological evaluation with MAID and MPATH ontology and definitive morphological diagnosis(es) for 2M + 2F per mouse line (10M + 10F for WT controls)
 - Image-enabled histopathology summary for each mouse line
4. Mouse line selection
 - 30 mouse lines chosen randomly from Sanger MGP pipeline with no in-life phenotype
 - 20 mouse lines chosen randomly from Sanger MGP pipeline with one or more in-life phenotypes

Histopathology Screen Pilot Project



Preliminary Results

| | | | Mutant lines with in-life phenotype | | Mutant lines with no in-life phenotype | | |
|----------------------|-----------------------|--------------------------------------|--|---|---|---|--|
| Cohort | Number of mouse lines | Spontaneous / Incidental findings(s) | Significant finding(s) associated with in-life phenotype | Significant finding(s) unlikely associated with in-life phenotype | Significant finding(s) likely association with genotype | Significant finding(s) unlikely association with genotype | Significant finding(s) with unannotated gene |
| WT | 2 | 2 | - | - | - | - | - |
| In-life Phenotype | 15 | 15 | 11 | 4 | - | - | - |
| No in-life Phenotype | 12 | 8 | - | - | 4 | 0 | 0 |
| | 29 | | | | | | |

So far:

1. Good concordance in % of mice with Spontaneous / Incidental Findings between WT and Mutants
 - Most are B6-related (hydrocephalus, microphthalmia) or high fat diet-related (hepatitis, gastritis)
2. In 11 / 15 lines (73%) with in-life phenotype we are contributing tissue-level phenotype data
3. In 4 / 12 lines (33%) with no in-life phenotype we have identified significant findings likely associated with genotype based on gene annotation

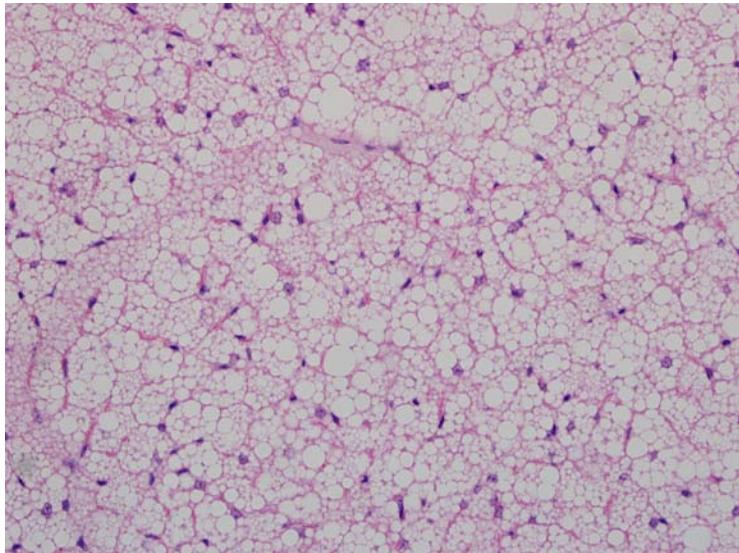
Histopathology Screen Pilot Project



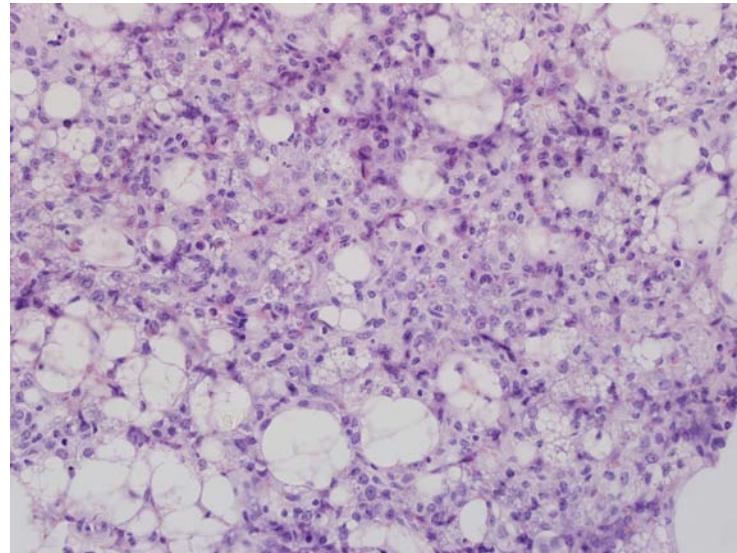
Preliminary Results

| | |
|--------------------------------------|---|
| Symbol Name ID | Efna1 ephrin A1 MGI:103236 |
| Go Annotation (Biological Processes) | Activation of MAPK pathway Angiogenesis |
| Morphological Diagnosis(es) | Hibernoma (2 of 4) |

WT brown fat (x400)



Mutant brown fat (x400)



Histopathology Screen Pilot Project



Preliminary Results

Symbol

Abhd5

Name

abhydrolase domain containing 5

ID

MGI:1914719

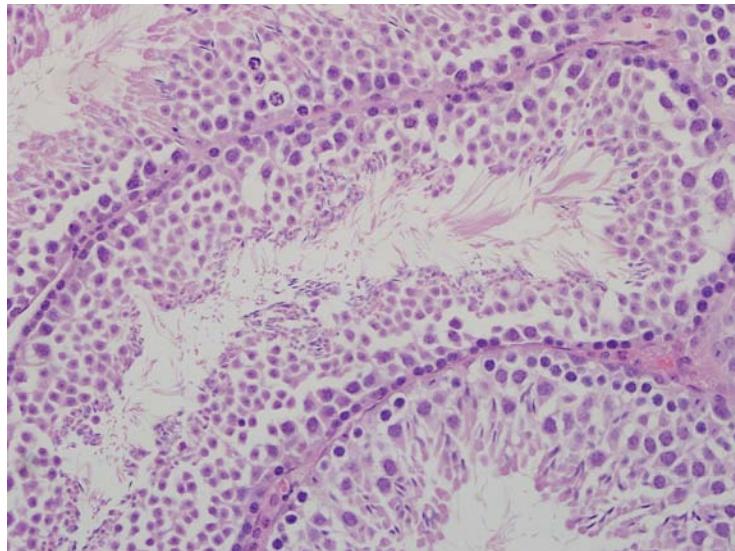
Go Annotation (Biological Processes)

Cell differentiation
Fatty acid metabolism
Lipid metabolism
Negative regulation of sequestering Triglyceride

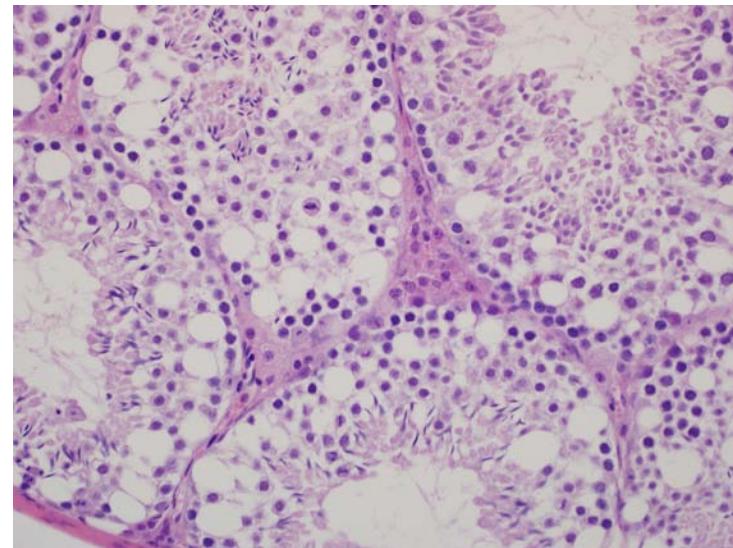
Morphological Diagnosis(es)

Diffuse sertoli cell vacuolation (2 of 2 males)

WT seminiferous tubules (x400)



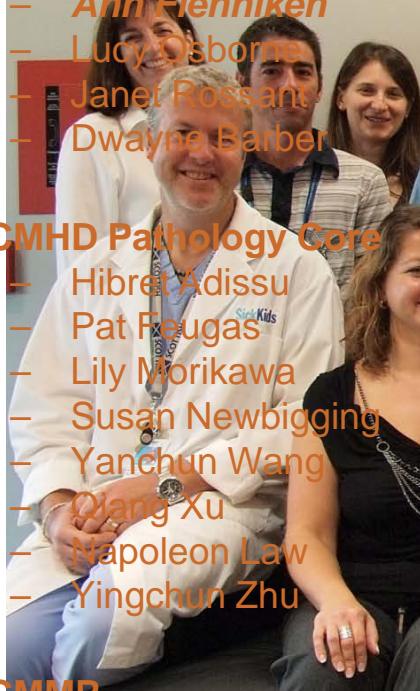
Mutant seminiferous tubules (x400)



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- Jason Learch

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